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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/902,953	07/11/2001	Achim H. Krotz	ISIS-4797	9234

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EXAMINER
SCHULTZ, JAMES

ART UNIT	PAPER NUMBER
1635	9

DATE MAILED: 11/20/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

FILE

Office Action Summary	Application No.	Applicant(s)	
	09/902,953	KROTZ ET AL.	
	Examiner	Art Unit	
	J. Douglas Schultz	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *03 September 2002* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-14* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-14* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Response to Arguments

Applicant's response filed September 3, 2002 has been considered. Rejections and/or objections not reiterated from the previous office action mailed June 13, 2002 are hereby withdrawn. The following rejections and/or objections are either newly applied or are reiterated and are the only rejections and/or objections presently applied to the instant application.

1. Claims 1-14 stand rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention, for the same reasons of record as set forth in the previous Office Action.

Applicants traverse the above rejection made in the Office action of June 13, 2002, made on the grounds that the term "bioequivalent" does not possess adequate written description in the specification as filed. Applicants argue that the specification as a whole, and that the passage of page 8 lines 3-5, which encompasses prodrugs, deletion derivatives and conjugates etc., enables the claims in reference to the term "bioequivalent".

Applicant's arguments have been fully considered but they are not persuasive. As stated in the previous Office action, the definition present in the specification of the term "bioequivalent", comprises a few "non-limiting" examples, but does little to clearly identify what

is embraced by said term. For example, Applicant argues that said term denotes those species that function as oligonucleotides in an organism; it is well known in the art that oligos are capable of specific binding to virtually any protein or ligand (e.g. aptamers), and as such, a bioequivalent of an oligo would encompass anything that binds specifically to any protein or ligand. Applicant clearly has no support for such broad contemplation. Given the breadth of said term, and the broad, explicitly non-limiting examples provided in the specification and Applicants' arguments, the term "bioequivalent" stands rejected for lack of written description.

2. Claims 1-5, 7-12, and 14 stand rejected under 35 U.S.C. 102(b) as being anticipated by Zhang et al. (U.S. Patent Number 6,258,600), for the same reasons of record as set forth in the previous Office Action.

The claims are drawn to formulations comprising oligonucleotides with base, sugar, linkage and 2' modifications and an antioxidant in bi- or multi-phasic solutions, wherein said antioxidant partitions to the aqueous phase, and to methods of preventing desulfurization using said formulations.

Applicant traverses the rejection of said claims under 35 USC 102(b) as being anticipated by Zhang et al. Applicant argues that the claimed invention can only be discerned by engaging in impermissible picking and choosing of the various combinations disclosed by Zhang et al., and

that one would have had at most very long odds of selecting the combination that would otherwise anticipate the invention of the above claims.

Applicant's arguments have been fully considered but they are not persuasive. The impermissible picking and choosing that Applicants' arguments are based on emanates from *In re Arkley* (455 F.2d 586, 587 (C.C.P.A. 1972)), a case where a generic chemical structure and all possible substitutions resulted in conservative estimates of over 230, 000 possibly claimed structures. In the instant case, Zhang et al., in discussing formulations of oligonucleotides, clearly identifies that "antioxidants are commonly added to emulsion formulations to prevent deterioration of the formulation", and lists 6 specific antioxidants, some of which partition to the aqueous phase as presently claimed. Col. 15, lines 35-42. Accordingly, the elements of the presently claimed invention are clearly set forth in Zhang et al., said elements are discussed in the same context as presently contemplated, i.e. preventing oxidation, and furthermore, in numbers not at all comparable to Applicants case citation. Thus, the elements are not scattered and unrelated, but are presented as a prepared formulation for preventing oxidation of oligos in bi-phasic solution. It is thus unclear how the disclosure of Zhang et al. forces one to pick and choose to discern the presently claimed formulation, when Zhang et al. so clearly lays out all the limitations of the above listed claims in cohesive discussion.

It is worth noting that Applicants' quotation of *In re Schaumann* is taken from the *minority* opinion of the lower court, an opinion *not* upheld by the C.C.P.A. Furthermore, Applicant's argument that Zhang et al. lacks any specific teaching that water soluble oxidants are

advantageous is not a consideration under 35 U.S.C. 102, which requires that the invention be substantially identical to be anticipated. Thus as outlined above, said claims stand rejected.

3. Claims 1-14 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Modi et al., in view of Zhang et al., Burt et al., and Baracchini et al. for the same reasons of record as set forth in the previous Office action.

Applicant traverses the rejection of the above claims as being obvious. Applicant argues that while Modi et al. discloses the use of several different antioxidants in biphasic micellar solution, that Modi et al. do not disclose the advantage of using water-soluble antioxidants over the use of oil soluble antioxidants, and that by stating that a preferred embodiment is tocopherol which is oil soluble, that the Modi patent actually teaches away from using water soluble antioxidants. Further Applicant argues that neither the Zhang et al., nor the Baracchini et al. patents are available as prior art under 35 U.S.C. 103 because the prior art and instant application are commonly owned. Finally Applicant argues that none of the cited references demonstrate the surprising finding that prevention of oxidation is better observed with water-soluble antioxidants as compared to oil-soluble antioxidants.

Applicant's arguments have been fully considered but they are not persuasive. In considering Applicant's allegation that water-soluble antioxidants deliver surprising results in preventing oxidation of oligos as compared to oil-soluble antioxidants, it is submitted that

despite Applicants' surprising finding, the combination of water soluble antioxidants in biphasic solution with oligonucleotides had been previously disclosed, both by Modi et al. and Zhang et al. as discussed in the previous Office action. Accordingly, Applicant's arguments are misdirected; the specific combination of water-soluble antioxidants in biphasic solution with oligonucleotides is considered anticipated, and was not the subject of the obviousness rejection of the prior office action. Had said combination been rejected for obviousness rather than anticipation, such arguments might be considered more relevant. The obviousness rejection was directed to the limitations comprising the specific antioxidants and oligo modifications of the claim set, rather than the generic claim of water-soluble antioxidants in biphasic solution with oligonucleotides. However, regarding these limitations, it is well known to one of ordinary skill in the art that oligonucleotides are water soluble, and would thus sequester to the aqueous component of a biphasic solution. It is therefore difficult to comprehend the surprise in finding that water-soluble species (e.g. oligos) are best protected from oxidation by water-soluble antioxidants, regardless of which water-soluble antioxidant species is used.

Furthermore, Applicants arguments that Modi et al. teaches away from using water soluble antioxidants is refuted by Modi et al., in the sentence prior to the identification of tocopherol as a preferred embodiment; ascorbic acid is identified as an embodiment of the Modi et al. patent, and is water soluble (col. 4, line 53). The invention of Modi et al. is directed to any pharmaceutical micellar composition which might encompass any oil or water soluble drugs, of which oligos are but one species; thus, the identification of tocopherol as a preferred embodiment (as opposed to the preferred embodiment as referenced in Applicants' arguments)

does not teach away at all from using antioxidants in biphasic solutions. To the contrary, Modi et al. clearly teaches that the use of one or more antioxidants in pharmaceutical compositions is usual in the art (col. 4, line 42-44), and identifies water-soluble antioxidants for use specifically. It appears unlikely that Modi et al. would teach away from using an embodiment that is specifically disclosed.

Finally, Applicants allege that Zhang et al. and Baracchini et al. are unavailable as prior art under 35 U.S.C. 103 because the prior art and instant application are commonly owned, and cites MPEP 706.02(k)(E) in support. Applicant is directed to the language of 35 U.S.C. 103, wherein paragraph (c) mandates that such a reading applies to prior art qualifying only under any of 102(e), (f), or (g). Both Zhang and Baracchini et al. qualify not only as 102(e), but also as 102(a) and 102(b) type art, respectively. The section of the MPEP relied upon by Applicant is directed to provisional 103/102(e) rejections; a more thorough discussion of relevant non-provisional rejections, of which the instant rejection is one, can be found at MPEP 706.02(l)(3). In this more thorough discussion, particularly in paragraph (B), it is made unequivocally clear that 102(e) art that also is eligible as 102(b) or 102(a) art may not be so disqualified. Therefore, Zhang et al. and Baracchini et al. were correctly relied upon by the examiner. Accordingly, the claims listed above stand rejected as being obvious over the prior art as outlined above.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to J. Douglas Schultz whose telephone number is 703-308-9355. The examiner can normally be reached on 8:00-4:30 M-F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, John L. LeGuyader can be reached on 703-308-0447. The fax phone numbers for the organization where this application or proceeding is assigned are 703-305-3014 for regular communications and 703-305-3014 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

J. Douglas Schultz, PhD
November 8, 2002

ANDREW WANG
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1600